REMARKS/ARGUMENTS

This responds to the issues presented in the Office Action of April 19, 2010, a Final Rejection, and accompanies a Request for Continued Examination.

Claims 41 and 42 have been amended to replace "is capable of allowing" by "allows".

New claims 43 and 44 have been added, specifying that the composition does not comprise an agent which adjusts the pH in the gut to greater than 7.5. This is based on page 2 lines 3-5 of the specification.

Addressing the objections in the Action, in sections 4 to 12 (35 U.S.C. §103) the Examiner objects to all pending claims, asserting that it would have been obvious to a skilled person to modify a bicarbonate composition of the type described by New in US 5,853,748 (hereafter "New") by adding propyl gallate (PG) or butylated hydroxy anisole (BHA), in view of US 5,206,219 (hereafter "Desai"). With respect, the Applicant disagrees. In particular, the Applicant believes that the Examiner has not given due weight to the arguments and factual evidence provided by the Applicant in previous submissions.

Thus, in order for a claim to be rejected under 35 U.S.C. 103, the claimed subject matter must have been obvious to a person of ordinary skill in the art. In other words, it must be the case that the skilled person would have arrived at the claimed subject matter in an obvious manner, starting from the prior art. To this end, it is not enough if a first prior art document discloses a product X that has most features of the claim, and a second prior art document discloses the missing feature Y. Rather, it must have actually been obvious to the skilled person to add feature Y to product X.

In this regard, it would clearly not be obvious to add feature Y to product X if so doing would ruin product X, i.e. no expectation of success. For instance, product X could be a gasoline-powered car engine and Y could be an oil additive for diesel engines. Would it be obvious to use Y in a gasoline engine? Clearly not, because no mechanic would dream of putting a diesel engine product into a gasoline engine, as he or she would know that it could have disastrous effects on the gasoline engine, because engines are very sensitive to the substances present in the engine oil. Accordingly, in this situation it would clearly not be obvious to add feature Y to product X.

Similar considerations apply to the present application.

Thus, the Examiner states in point 7 that

"New teaches a pharmaceutical composition of (i) a biologically active proteinaceous material, oligonucleotide or analogue thereof or polysaccharide; (ii) a bile acid or salt; and (iii) an agent having the ability to adjust the pH of the gut to a value of from 7.5 to 9. New teaches specific example of macromolecular principle (insulin), a bile acid (chenodeoxycholic acid) and an additive that buffers the gut to pH 7.5 – 9 (sodium bicarbonate, example 4)..."

In the last sentence of point 7 of the Office Action the Examiner acknowledges that New does not teach to add propyl gallate (PG) or butyl hydroxyl anisole (BHA) to its compositions (as is required by claim 1). However, in point 8 the Examiner goes on to say that Desai mentions both PG and BHA among possible antioxidants. Thus, the Examiner's position is that New discloses product X and Desai discloses feature Y. The Examiner argues that it would have been obvious to add PG or BHA to the New composition, i.e. to add feature Y to product X.

However, the Applicant strongly believes that no person of ordinary skill in the art would have contemplated taking this step, let alone think it was obvious. That is because, just as putting a diesel engine product into a gasoline engine would risk ruining the engine, adding PG or BHA to the New composition would risk ruining the composition. (In fact, as noted below, it has been shown as a matter of fact that adding PG or BHA to the New composition does indeed ruin it.)

Thus, as noted by the Examiner on page 5 of the Office Action (lines 5 to 9), New explains that the way its compositions work is by maintaining the components as a solution, and that the whole purpose of the composition (to enhance bio-absorption by acting on the epithelial cells) may not be achieved when the acid is in the solid, i.e. non-aqueous form. In other words, unless it is able to form an aqueous solution, the New composition does not work.

However, just as engines are sensitive to the substances present in the engine oil, the success of the New composition (i.e. its ability to form an aqueous solution) will be sensitive to the substances present in the composition. That is why a skilled person would not have contemplated (let alone thought obvious) adding PG or BHA to the New composition.

Thus, firstly, PG and BHA are known in the art as additives (antioxidants) for non-aqueous environments. For instance, their main known use us to prevent rancidity in oils and fats, as proven by the extracts from the Handbook of Pharmaceutical Excipients filed on January 19, 2010 (see point 7 of each extract). Further, Desai itself reinforces this, because PG and BHA are mentioned in Desai specifically as possible additives for the lipid solvent – column 5 line 16 notes that the relevant additives must be "oil soluble". If a skilled person wanted to add a preservative to a composition intended to form an aqueous solution, he or she would clearly have selected one of the many well-known water-soluble additives, rather than PG or BHA which are known to be very poorly soluble in water.

Secondly, the Applicant has filed evidence proving as a matter of fact, that adding PG or BHA does indeed ruin the New composition by preventing formation of the crucial aqueous solution. This evidence was set out in the Declaration dated April 2, 2009 (filed at the USPTO on May 1, 2009), which reported that adding PG or BHA resulted in a turbid dispersion, which persisted even after incubation at 60 °C. This demonstrates exactly why a person of skill in the art would simply not have considered adding PG or BHA to the New composition.

Accordingly, just as no mechanic would consider adding a diesel product to a gasoline engine, no pharmaceutical chemist would have considered adding PG or BHA to the New composition. Thus, it is respectfully submitted that the objection that the claimed subject matter was obvious from New and Desai should be withdrawn.

It is believed that the objection under 35 U.S.C. §103(a) can no longer be maintained in the light of the above comments alone. Nonetheless, for completeness, the Applicant also offers the following additional comments.

Firstly, the Applicant wishes to draw particular attention to dependent claims 36 and 37, to which the above arguments apply even more so. Claims 36 and 37 specify that the composition of the invention must be soluble in water. As noted above, it has been shown that the composition suggested by the Examiner to be obvious (the New composition with PG or BHA added to it) would not be soluble. Accordingly, even in the situation suggested by the Examiner (where the skilled person had gone ahead and added PG or BHA to the New composition despite knowing that would ruin it by prejudicing its solubility in water), the resulting product would still not be covered by claim 36 or 37.

Secondly, the Applicant also wishes to draw particular attention to new claims 43 and 44, to which the above arguments again apply even more so. Claims 43 and 44 specify that the composition does not comprise an agent which adjusts the pH in the gut to greater than 7.5. It is, of course, an essential feature of New that sodium bicarbonate (or other pH adjuster) is present, in order to adjust the pH to greater than 7.5, since the invention as proposed by New will not work in the absence of such a buffering agent.

The subject matter of claims 43 and 44 is therefore different from New, not only because it contains PG or BHA, as the Examiner states, but also because it does not contain an additive that buffers the gut to pH 7.5 - 9. PG is demonstrably not an agent which is capable of adjusting the gut to pH 7 – 9, and one skilled in the art would never consider it to be such, since under normal circumstances it is highly insoluble in aqueous media such as those which one would expect to find in the gut; similar considerations apply to BHA (as proven by the extracts from the Handbook of Pharmaceutical Excipients filed on January 19, 2010).

Furthermore, the PG employed in the instant application has not been added in order to buffer the pH of the gut to between 7.5 and 9. Indeed, claim 1 specifically states that the pH at which the formulation acts is below pH 7. The fact that Desai has combined PG with insulin is not relevant because Desai has used PG as a preservative (not a pH-adjusting agent) and as such it will be employed only at low concentrations.

Thirdly, the Applicant offers the following comments in response to some of the specific points made in the Office Action. These are set out in sections using numbering corresponding to that of the Office Action. For brevity the comments focus on the additive PG, but they also apply correspondingly to BHA too.

Items 7 to 9

The Examiner states that New teaches that increasing the solubility of the bile salt will enhance its permeation activity (first full sentence on page 4 of the Office Action). The Examiner also states that it would have been obvious to one skilled in the art to add a preservative to the insulin formulation in order to improve the stability of the insulin in the formulation (point 10 on page 6 of the Office Action). However, the present invention relates to the Applicant's surprising finding that PG and BHA improve the solubility of one component of the formulation. The Applicant contends that this would not have been obvious, since that is not

a function that PG or BHA were normally known to perform. Stability and solubility are two very different properties, and agents that affect one do not necessarily affect the other.

Furthermore, even if a person of ordinary skill in the art had attempted to add PG to a formulation of bile salt to act as a preservative, he or she would have employed it in small quantities – the extract from the Handbook of Pharmaceutical Excipients filed on January 19, 2010 confirms that it was typically used at concentrations of up to 0.1 % w/v, and sometimes up to 0.01 or 0.002 % (see section 7 thereof). Such low levels of PG are insufficient to enhance the solubility at pH below 7, so once again, even if the Examiner's suggestion were correct (which we do not believe to be the case), one skilled in the art would not have arrived at a workable version of the instant composition through a combination of New and Desai, because an insufficient quantity of PG would have been employed.

The Examiner has noted that Desai states that adjuvants for preserving formulations are antioxidants like BHA, BHT alpha-tocopherol and PG, and that these are commonly used in pharmaceutical compositions of insulin (see point 8 of the Office Action). In point 10 the Examiner states that it would have been obvious to add these to the formulation of New, in order to extend the shelf-life. However, as has already been testified in the declaration dated April 2, 2009 (filed at the USPTO on May 1, 2009), addition of PG to a preparation containing bicarbonate results in an insoluble turbid dispersion. In light of this finding, one skilled in the art would not have been motivated to remove the sodium bicarbonate, even if they thought that the bicarbonate was causing the problem, since New teaches that the presence of bicarbonate is essential to adjust the intestinal pH to between 7.5 and 9, in order to maintain the solubility of the bile salt in the gut. Thus, any attempt of a skilled person to prepare a formulation based upon New but containing high levels of PG would have failed.

One skilled in the art would not have thought that the PG itself could keep the bile salt in solution, since PG is not a known solubilizing aid, and it is not capable of maintaining the pH at a high level in the gut. The non-obviousness of the present invention relates to the use of additives such as PG to maintain non-conjugated bile acids or salts in solubilized form at gut pH levels without use of bicarbonate or any other pH adjuster. This is a key distinction between New and the instant application, and one could not have derived one from the other.

Item 10

The Examiner states that since a combination of sodium bicarbonate (additive) increased the solubility of the bile acid, then the combination of a known antioxidant into the formulation would also have the same solubility (see the sentence bridging pages 6 and 7 of the Office Action). The Applicant points out, however, that this does not necessarily follow, and there are many examples in pharmaceutical practice where incompatibility is observed between different components, which impairs the behavior of the formulation as a whole. The declaration dated April 2, 2009 (filed at the USPTO on May 1, 2009) demonstrates that there is indeed such an incompatibility when bicarbonate and PG are added together in the same formulation, leading one to conclude that the Examiner's assertion is incorrect, and that any supposition which follows from this assertion is also incorrect.

Item 11

On page 14 the Examiner states that there is no evidence that (a) and (b) did not form a soluble formulation without the presence of the additive (c). However, the data in Figure IB accompanying Example 3 of the present application do provide such evidence. Globular proteins in general are known to have good aqueous solubility over a range of pH levels, but do not display any propensity to act as solubilizing aids. In Figure IB it is demonstrated that chenodeoxycholate alone is insoluble at pH 6.5 and pH 5 over a range of concentrations, and it is reasonable to expect that similar behavior will be seen even when a globular protein is present. In Figure IA, however, it can be seen that combination of chenodeoxycholate with PG results in complete dissolution under the same conditions.

Item 12

At page 11 of the Office Action, the Examiner raises an objection based on the notion that the claims merely require the additive (c) to be capable of allowing the bile acid or salt to remain in solution. The Examiner suggests that the function therefore may or may not occur. Claims 41 and 42 are the relevant claims. Both have now been amended to specify that the additive actually allows this to happen (rather than merely being capable of allowing it to happen). Accordingly, this point of the Office Action and any supposition based on it no longer applies.

At page 12 of the Office Action, the Examiner states that the "132 declaration" does not provide any evidentiary basis. Presumably the Examiner is referring to the declaration dated 6 January 2010. With respect, the Applicant disagrees. The declaration provides evidence of the educated opinion of one skilled in the art, and as such it is "evidence that must be considered" according to the MPEP quote given by the Examiner. Moreover, the reasoning in the declaration is clearly based on matters of fact, such as the specific teaching of New and Desai (respectively '748 and '219 – see points 4 and 7 of the declaration), the known solubility of PG and BHA (point 12 of the declaration) and what actually happens when PG or BHA is added to the New composition (point 13 of the declaration). Accordingly, the declaration should be given due consideration.

Favorable reconsideration of this application is respectfully requested.

Respectfully submitted,

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